REMARKS

Claims 7-8 are pending herein and stand rejected.

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 7 and 8 under 35 U.S.C. 103(a) as being unpatentable over Gold *et al.* (U.S. 5,270,163) in view of Tullis (WO 88/09810) and Ferns *et al.* (Science 1991, vol. 253, pages 1129-1132). The Examiner contends that Gold *et al.* teach a method for identifying nucleic acid ligands by a process of *in vitro* selection and amplification; that Tullis teaches nucleic acid conjugates comprising an antisense conjugated to a solubility modifying moiety that may be hydrophobic; and that Ferns *et al.* teach that inhibition of PDGF is a possible approach for prevention of restenosis following angioplasty.

The Examiner has deemed Applicants' arguments made in the prior response to this identical rejection unpersuasive. Specifically, the Examiner contends that, in contrast to Applicants' arguments, that there is a reasonable expectation of success for the present invention. The Examiner acknowledges the differences between the nucleic acids of Tullis, which act through Watson-Crick base pairing, and nucleic acid ligands, which interact through a three dimensional interaction. However, the Examiner contends that despite these differences, the "reasonable expectation of success lies in the teachings of the art that nucleic acid conjugates are known to increase the uptake of nucleic acids." Office Action, page 3. The Examiner also contends that "the art teaches that conjugation of nucleic acids to compounds that increase their solubility and uptake was well-known in the art prior to the time of the invention." *Id.* The Examiner also quotes from Applicants' argument with respect to the written description rejection where Applicants note that the art with respect to conjugating lipophilic compounds and/or high molecular weight compounds to therapeutically active compounds is very well developed, as supporting the Examiner's contention that a person of ordinary skill in the art would have a reasonable expectation of success in combining the references of Gold et al. and Tullis to make conjugates of nucleic acid ligands and non-immunogenic, high molecular weight compounds such as PEG.

Applicants traverse this rejection, respectfully disagreeing with the Examiner's contention that success was predictable. Below, several lines of evidence are presented, rebutting the Examiner's finding of a reasonable expectation of success.

Applicants first wish to discuss the Examiner's above-noted assertion that the "reasonable expectation of success lies in the teachings of the art that nucleic acid conjugates are known to

increase the uptake of nucleic acids" and "the art teaches that conjugation of nucleic acids to compounds that increase their solubility and uptake was well-known in the art prior to the time of the invention." *Id.* As the Examiner clearly realizes, the Tullis reference teaches "novel nucleic acid conjugates for inhibiting **intracellular** mRNA maturation . . .[c]onjugates comprise a relatively short oligonucleotide sequence, a linking group, and a group with modifies the HLB (hydrophilic lipophilic balance) to provide an amphiphilic product." *See* WO 88/09810, page 41, lines 1-8 (emphasis added). Applicant respectfully directs the Examiner's attention to the Tullis' teaching of the nucleic acid conjugates for affecting **intracellular** events. Applicants also respectfully direct the Examiner's attention to the sentence immediately following the previous quotation, which reads, "the amphiphilic nature of the product [nucleic acid conjugate] aids in the transport of the conjugate across the cellular membrane, and can provide additional advantages, such as increasing aqueous or liquid solubility of nucleic acid derivatives, e.g., use of an amphiphilic group to enhance water solubility of long chain methyl phosponates and stabilizing normal nucleic acids to exonuclease digestion." *Id.*, at lines 9-15. Applicants note that the teaching is limited to such conjugates having increased ability to be transported across the cellular membrane, and to increase the water solubility and stability of the conjugate to exonuclease digestion.

In contrast, Applicants teach, among other advantages, increasing the plasma half life of Applicants' PDGF nucleic acid ligands. Claim 7 reads, in relevant part, "A method for **improving the pharmacokinetic properties** of a PDGF Nucleic Acid Ligand." Applicants also respectfully direct the Examiner's attention to the Specification, where Applicants state, "'Improved Pharmacokinetic Properties' means that the PDGF Nucleic Acid Ligand covalently linked to a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound or in association with a Lipid Construct **shows a longer circulation half-life in vivo** relative to the same PDGF Nucleic Acid Ligand not in association with a Non-Immunogenic, High Molecular Weight Compound or Lipophilic Compound or in association with a Lipid Construct." See Specification, page 24, lines 3-8. Further, PDGF is a growth factor, e.g., it occurs extracellularly. To interact with PDGF, in other words, the Nucleic Acid Ligands of the invention do not have to enter the cell. Applicants make this clear in the Specification: "A few instances have been reported where researchers have attached antisense oligonucleotides to Lipophilic Compounds or Non-Immunogenic, High Molecular Weight Compounds. Antisense oligonucleotides, however, are only effective as **intracellular** agents." See Specification, page 7, lines 24-26 (emphasis added).

Thus, it is clear that Applicants' invention is directed towards molecules with a non-intracellular target (e.g., PDGF) that have an extended plasma half-life. In contrast, Tullis teaches an antisense oligonucleotide conjugate, which is directed to an **intracellular** target. Tullis teaches that the benefits of the amphiphilic molecule are limited to those that aid in the transport of the antisense oligo across the cell membrane, to increase the intracellular concentration of the antisense oligo: "the amphiphilic nature of the product [nucleic acid conjugate] aids in the transport of the conjugate across the cellular membrane, and can provide additional advantages, such as increasing aqueous or liquid solubility of nucleic acid derivatives." Thus, it is clear that Tullis does not teach or suggest that the plasma half life of a nucleic acid molecule can be extended by conjugating to a Non-Immunogenic, High Molecular Weight Compound, e.g., a PEG molecule, or a Lipophilic Compound. Neither does Tullis suggest that such conjugates would be useful for targets of the nucleic acid molecule that reside **outside** of the cell. Thus, Applicants respectfully submit that the teachings of Tullis with respect to nucleic acid conjugates are limited to use of a Non-Immunogenic, High Molecular Weight Compound, e.g., a PEG molecule, or a Lipophilic Compound in order to assist in transport across cell membranes for nucleic acids that are active intracellularly. Applicant respectfully submits that as such, there is no teaching or suggestion in the combination of Tullis and Gold et al. to extend the plasma half life of a nucleic acid molecule by conjugating to a Non-Immunogenic, High Molecular Weight Compound, e.g., a PEG molecule, or a Lipophilic Compound, nor is there a teaching that such conjugates would be useful for targets of the nucleic acid molecule that reside **outside** of the cell. Accordingly, Applicants submit that there is no prediction of success for the instant invention from the Gold *et al.* teachings of a method for identifying nucleic acid ligands by a process of *in vitro* selection and amplification and the Tullis teachings of nucleic acid conjugates comprising an antisense conjugated to a solubility modifying moiety that may be hydrophobic. Reconsideration is respectfully requested.

Moving on to another point, Applicants would also like to rebut the Examiner's argument that Applicants' argument with respect to the written description rejection (in Applicant's previous response), where Applicants note that the art with respect to conjugating lipophilic compounds and/or high molecular weight compounds to therapeutically active compounds is very well developed, as supporting the Examiner's contention that a person of ordinary skill in the art would have a reasonable expectation of success in combining the references of Gold et al. and Tullis to make conjugates of nucleic acid ligands and non-immunogenic, high molecular weight compounds such as PEG. Applicants quote from their previous response:

FDA-approved drugs include the following approved by 2005: ABELCET® (liposomal formulation of amphotericin B) sold by Enzon, AMBISOME® (liposomal amphotericin B) sold by Gilead Sciences, Inc., and Fujisawa Healthcare, AMPHOTEC® (lipid-based colloidal dispersion of amphotericin B) InterMune Pharmaceuticals, Inc., DAUNOXOME® (liposomal form of daunorubicin) sold by Gilead Sciences, DEPODUR (morphine sulfate extended-release liposome injection) sold by Endo Pharmaceuticals, Inc., and SkyePharma plc, DOXIL® (liposomal formulation of doxorubicin hydrochloride) sold by Alza (subsidiary of Johnson & Johnson), ESTRASORB™(Estradiol topical emulsion) sold by Novavax, Inc. and King Pharmaceuticals, Inc., IMAGENT® (perflexane lipid microspheres) sold by Alliance Pharmaceutical Corp., Cardinal Health, Inc. and InChord Communications, Inc., **MACUGEN® (pegaptanib sodium injection; pegylated anti-VEGF aptamer)** sold by Eyetech Pharmaceuticals, Inc. and Pfizer, PEGASYS® (peginterferon alfa-2a) sold by Roche and Nektar Therapeutics, Inc., PEG-Intron™ (pegylated version of interferon alfa-2b) sold by Enzon, Inc., and Schering-Plough Corp. (*see* Biotechnology Industry Organization, www.bio.org). Each of these new drugs have been in development for a number of years, indicating this art area's longstanding mature standing.

Applicants note that their statement that the art relating to conjugating lipophilic compounds and/or high molecular weight compounds to therapeutically active compounds is very well developed. However, Applicants note that this statement is with respect to the lipophilic compounds/high molecular weight moieties only. The only nucleic acid ligand (i.e., aptamer) on this list is MACUGEN®, and this therapeutic was approved in 2004, well past the priority date of the instant application. Applicant respectfully submits that while this list shows maturity in the art with respect to lipophilic compounds and/or high molecular weight compounds, such maturity does not *per se* suggest that it can be predicted with reasonable expectation of success that combinations of the same with nucleic acid ligands would lead to successful therapeutic compounds.

Applicants have additional information, i.e., publications, which discuss the state of the art at the time of the present invention. Applicants note that when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to: (A) The claimed invention must be considered as a whole; (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and (D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

In addition to the arguments made previously, in Applicants' previous Amendment and Remarks, Applicants have additional remarks regarding the state of the art with respect to whether a skilled artisan would expect a successful association of a PDGF nucleic acid ligand

and a non-immunogenic, high molecular weight compound or lipophilic compound. In a review article published contemporaneously with the priority date of the present application, i.e., Stull and Szoka, "Antigene, Ribozyme And Aptamer Nucleic Acid Drugs: Progress And Prospects", *Pharmaceutical Research*, 12:4 465-483 (1995), the authors discuss how the small size of aptamers are a drawback to their use as therapeutics. We note that "aptamer" is another name for nucleic acid ligands of the invention. Importantly, the authors teach that although "cationic liposomes are effective for *in vitro* delivery of nucleic acid drugs and for *in vivo* gene transfer", cationic liposomes "to date have not been found useful for delivery of the low molecular weight nucleic acid drugs described in this review [i.e., antigens, ribozymes, and aptamers]" *Id.*, p. 478. Accordingly, Applicants submit that this teaching shows that those of skill in the art did not have a reasonable expectation of success for the usefulness of a complex comprised of a PDGF nucleic acid ligand and a non-immunogenic, high molecular weight compound or lipophilic compound, as the authors directly state that liposome formulations with aptamers have not been successful.

Another reference, a more recent one, Veronese and Pasut, "PEGylation, successful approach to drug delivery", *Drug Discovery Today*, 10:1451-1458 (2005), provides some information on the state of the art with respect to PEGylation. Importantly, this reference teaches, even as of 2005, that "[u]nfortunately, the PEGylation of proteins is often accompanied by a loss of biological activity", although often "this [loss] is compensated for by the prolonged body-residence time [provided by higher molecular weight conjugates]." *Id.* at 1455. As discussed in our previous Office Action Response, and acknowledged by the Examiner, nucleic acid ligands are akin to proteins, in that their activity is due to their three-dimensional conformation, rather than Watson-Crick interactions. Thus, per the Veronese reference, one of skill in the art would expect a loss of activity for a nucleic acid ligand upon PEGylation. For large sized proteins, this loss is often compensated for by an increase of body residence time, according to the reference. However, Veronese also teaches difficulty in PEGylating smaller molecules, as smaller molecules can not be loaded with as many PEG molecules as larger proteins. *Id.* at 1456. Lower loading means a smaller molecule with decreased body residence times. Since Veronese teaches that increased body residence time is key to balancing the loss of biological activity caused by PEGylation, and Veronese also teaches that smaller molecules cannot be "loaded" as heavily with PEG molecules, Applicants submit that even as of 2005, the art is does not provide an expectation of success with respect to using PEG to improve the pharmacokinetics of smaller (non-protein) drugs.

Summarizing Applicants' above arguments, Applicants submit that there is no prediction of success for the instant invention from the Gold *et al.* teachings of a method for identifying nucleic acid ligands by a process of *in vitro* selection and amplification and the Tullis teachings of nucleic acid conjugates comprising an antisense conjugated to a solubility modifying moiety that may be hydrophobic. Applicants submit that there no teaching or suggestion in the combination of Tullis and Gold *et al.* to extend the plasma half life of a nucleic acid molecule by conjugating to a Non-Immunogenic, High Molecular Weight Compound, e.g., a PEG molecule, or a Lipophilic Compound, nor is there a teaching that such conjugates would be useful for targets of the nucleic acid molecule that reside outside of the cell. Further, Applicant respectfully submits that while Applicants' list of approved conjugated drugs (as of 2005) shows maturity in the art with respect to lipophilic compounds and/or high molecular weight compounds, such maturity does not *per se* suggest that it can be predicted with reasonable expectation of success that combinations of the same with nucleic acid ligands would lead to successful anti-PDGF therapeutic compounds. With respect to the state of the art, the teachings of Stull and Szoka show that cationic liposomes "to date have not been found useful for delivery of the low molecular weight nucleic acid drugs described in this review [i.e., antigens, ribozymes, and aptamers]", indicating that a skilled artisan would not have an expectation of success for the present invention. The Veronese reference teaches that increased body residence time is key to balancing the loss of biological activity caused by PEGylation, and further teaches that smaller molecules cannot be "loaded" as heavily with PEG molecules, showing that even as of 2005, the art does not provide an expectation of success with respect to using PEG to improve the pharmacokinetics of smaller (non-protein) drugs.

Reconsideration is respectfully requested.

If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117 if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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